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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,105	01/16/2001	Donald S. Karanewsky	480140.442C1	8244

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,105	KARANEWSKY ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-153* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-24* is/are rejected.

7)☒ Claim(s) *25-153* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 10/10/03, claims 1-14 have been cancelled, and claims 24-153 added. Claims 15-153 are now pending.

Applicants' arguments filed 10/10/03 have been considered and found persuasive in part. The previously imposed §112 first paragraph rejection is withdrawn. In addition, the "ODP" rejection of claim 1 over application Serial No. 09/745204 is withdrawn. However, the "ODP" rejection of claim 1 over U.S. Patent No. 6,197,750 is maintained.

✧

Claim 24 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,197,750. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genera for the case of $R^{1'}$ (instant application) representing hydrogen. In response to this, applicants have filed a terminal disclaimer over USP 6,544,951. However, that terminal disclaimer is not effective to overcome this ground of rejection.

✧

35 U.S.C §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

. . . .

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

Claim 18 asserts that ischemic injury can be "prevented". However, this has not been shown to be the case. What has been shown is a 30% reduction in infarct size. This may actually be regarded as a kind of failure, at least insofar as 35 USC §101 is concerned. The result obtained provides evidence that despite treatment, there was a significant increase in infarct size relative to what would be expected if the treatment had been 100% effective. The term "prevention" implies that for a given population of test subjects, the treatment is not only 100% effective, but is 100% effective in 100% of the test subjects. This has not been shown, and moreover, the evidence supports the conclusion that the claimed compounds are not effective to prevent ischemic injury.

There is an argument to be made for a claim drawn to a method of mitigating ischemic injury, but as the language now stands, the rejection is justified.

Claim 18 is also rejected under 35 USC 112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

✧

Claims 15-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that one of the claimed compounds is effective to reduce infarct size, if given immediately following arterial occlusion. However, this does not amount to a demonstration that any and all "inflammatory" conditions can be successfully treated. Inflammatory conditions would include the following: meningitis, salpingitis, septic shock, respiratory diseases, inflammatory conditions, arthritis, cholangitis, colitis, encephalitis, endocerolitis, hepatitis, pancreatitis, hypersensitivity, multiple sclerosis, osteoporosis, Paget's Disease, neurodegenerative disease, Alzheimer's disease, and Parkinson's disease. It is also asserted that the compounds can be used to treat autoimmune disease. It is also asserted that the claimed compounds will be effective to expand hematopoietic cell populations.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Consider the following:

- Frost Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNFα and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.

- Meyers K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an anti-inflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).

- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.

- Brennan (*Clinical and Experimental Immunology* **81**, 278-85, 1990) discloses that TGF-β was effective to inhibit IL-1β production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF-β. The IL-1β production was not inhibited if the TGF-β was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1β when used prior to stimulation of cells (which stimulation produces the IL-1β), attempting to inhibit production of IL-1β by using agent "X" after stimulation of the cells leads to "unpredictable" results.

- Paris (*Journal of Infectious Diseases* **171**, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

Thus, attempting to extrapolate from *in vitro* ICE inhibition to treatment of human disease leads to "unpredictable" results; undue experimentation would be required to practice the methods of claims 15-23. It is suggested that each of the method-of-use claims be cancelled.

If it is well known in the art that caspase inhibition is effective to inhibit apoptosis, and if a reference indicating this is made of record, the possibility exists that the following claim might be enabled (the term "apoptosis" is used on p. 32):

> *A method of inhibiting apoptosis comprising administering to a patient in need thereof a compound according to claim 1 for a time and under conditions effective to inhibit a caspase.*

Accordingly, "undue experimentation" would be required to practice the claimed invention.

✧

Claims 15-23 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-23 are dependent on a cancelled claim.

Claim 18 is indefinite as to the manifestations of a successful treatment. If a physiologist were presented with a rat that had been "treated" with one of the claimed compounds, what would he see; how would he assess "success"...? Is "success" limited

to a demonstration that a reduction of infarct size had occurred, or are there other manifestations? For example, would there be histological changes in cardiac tissue, or decreased enzyme levels in the bloodstream? Then there is the matter of neurological damage. Suppose, for example, that a rat were treated with one of the compounds, and a 30% reduction of infarct size occurred. But suppose also that, despite the reduction of infarct size, significant neurological damage had occurred, as demonstrated histologically in hippocampus tissue, and also in the ability of the rat to "negotiate" a maze. Would this be considered a successful treatment?

✹

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1600